

Thiazide Diuretics and the Risk of Gallbladder Disease Requiring Surgery in Women

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Background: Previous studies have suggested that thiazide diuretic use increases the risk of cholecystitis.

Methods: We prospectively examined the association between thiazide use and cholecystectomy, a surrogate for symptomatic cholelithiasis, in a cohort of 81 351 US women who were aged 30 to 55 years in 1980 and followed up to 2000. Regular use of thiazide diuretics was assessed at baseline by asking the participants to report whether they currently took "any of the following medications in most weeks" and listing "thiazide diuretics (eg, Diuril and Hydrodiuril)" among other drugs. Respondents were also requested to report the duration of thiazide diuretic use. Assessment of thiazide diuretic use was updated in 1982, 1988, 1994, 1996, and 1998. Cox regression was used to adjust simultaneously for other potential risk factors for cholecystectomy.

Results: During follow-up, 8607 women reported un-

dergoing a cholecystectomy. A modest positive relation between the use of thiazide diuretics and cholecystectomy was observed. Compared with never users of thiazide diuretics, the multivariate relative risk of cholecystectomy for past users was 1.16 (95% confidence interval, 1.08-1.24) and the multivariate relative risk for current users was 1.39 (95% confidence interval, 1.29-1.50).

Conclusions: These findings are compatible with the hypothesis that the use of thiazide diuretics increases the risk of symptomatic cholecystitis. However, we cannot rule out the possibility that our results are in part explained by unconsidered factors related to the indication for antihypertensive therapy or by differences in medical surveillance between users and nonusers of thiazide diuretics.

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T HIAZIDE DIURETICS ARE widely used in the treatment of hypertension and cardiovascular disease.¹ Some experimental evidence in humans suggests that thiazide treatment increases biliary cholesterol saturation,² the main determinant of cholesterol gallstone development.³ Epidemiologic data concerning the association between thiazide diuretics and gallbladder disease are sparse and available studies have provided inconclusive findings. In 2 case-control studies^{4,5} recent thiazide use was associated with a statistically significant 2-fold increase in risk of acute cholecystitis. In contrast, 2 other case-control studies,^{6,7} one focusing on acute cholecystitis⁶ and the other considering gallstones as an end point,⁷ reported no association with recent thiazide diuretic use. Similarly, 1 case series involving patients with acute pancreatitis⁸ found that diuretic use

did not differ between the subgroup of patients with gallstones and the subgroup without gallstones. Thus, the association between use of thiazide diuretics and gallbladder disease remains unresolved. To help address this issue, we examined prospectively thiazide diuretic use in relation to risk for cholecystectomy, a surrogate for symptomatic cholelithiasis, during 20 years of follow-up in a large cohort of US women. We addressed whether noncausal mechanisms may have accounted for any observed association.

METHODS

STUDY POPULATION

In the Nurses' Health Study, 121 700 married female nurses aged 30 to 55 years completed a mailed questionnaire on their medical history and lifestyle characteristics in 1976. Every 2 years, follow-up questionnaires were sent

to update information on potential risk factors and to identify newly diagnosed illnesses. Starting in 1980, the questionnaire included an assessment of medication use. This analysis is based on the 81351 women who answered the 1980 questionnaire and did not have a cholecystectomy performed or cancer diagnosed before 1980. All study participants provided informed consent and this study was approved by the institutional review board on the use of human subjects in research of the Brigham and Women's Hospital in Boston, Mass.

ASSESSMENT OF THIAZIDE DIURETIC USE

Regular use of thiazide diuretics was first assessed in 1980 by asking the participants to report whether they currently took "any of the following medications in most weeks" and listed "thiazide diuretics (eg, Diuril, Hydrodiuril)" among other drugs. If the answer was yes, the participant was considered a thiazide diuretic user. Participants who did not indicate regular current thiazide diuretic use in 1980 were defined as nonusers. Respondents who indicated regular current thiazide diuretic use in 1980 were also requested to report the number of years they had taken thiazide diuretics prior to 1980.

Assessment of regular thiazide diuretic use was updated in 1982, 1988, 1994, 1996, and 1998. In 1988, the question was worded "Are you currently taking any of the following medications at least once a week" and listed "thiazide diuretics (eg, Diuril, Hydrochlorothiazide, Dyazide, Moduretic)" among other drugs. In 1994, 1996, and 1998, participants were asked to indicate whether they had used thiazide diuretics regularly in the past 2 years. Reasons for thiazide diuretic use were not assessed. However, the main indication for thiazide diuretics is hypertension.¹

IDENTIFICATION OF CASES OF CHOLECYSTECTOMY

We inquired about occurrence and date of cholecystectomy on each biennial questionnaire starting in 1980. A validation study of the self-report was conducted in a random sample of 50 nurses who reported a cholecystectomy in 1982. Forty-three of the 50 nurses who responded reiterated their earlier report, and the surgery was confirmed in all 36 for whom medical records could be obtained.⁹ In our main analysis we used cholecystectomy as our primary end point. In an alternate analysis, we considered cholelithiasis as an end point by limiting the analysis to cases of newly symptomatic but unremoved gallstones that occurred during the 1982 to 1984 and 1984 to 1986 follow-up intervals among the women who did not have a cholecystectomy in the same 2-year interval. This analysis addressed the association between thiazide diuretic use and less severe forms of gallstone disease.

DATA ANALYSIS

We calculated person-time of follow-up for each participant from the date of return of the 1980 questionnaire to the date of cholecystectomy, cancer, date of last questionnaire return, death, or the end of the study period in 2000, whichever came first. Using 1980 as the baseline of the follow-up period, women were divided into 2 categories according to their current use of thiazide diuretics: nonusers and users. In a separate analysis using 1982 as the baseline, our data allowed us to subdivide the group of users into past and current users, thereby arriving at 3 categories of thiazide diuretic use: never users, past users, and current users.

To account for changes in thiazide diuretic use over time, our primary analyses were conducted using the most recent thia-

zide diuretic use as recorded on the biennial questionnaires. In addition, we evaluated cholecystectomy risk according to the number of years of regular thiazide diuretic use (1 year, 2-4 years, 5-9 years, 10-14 years, and ≥ 15 years), with an update for this variable every 2 years. For example, if a woman began reporting thiazide use on the 1982 questionnaire and continued taking thiazide diuretics through 1988, she was assumed to have taken thiazides for 6 years in 1988. We also examined cholecystectomy risk according to the number of years since discontinuation of regular thiazide diuretic use (≥ 15 years ago, 10-14 years ago, 5-9 years ago, 2-4 years ago, and 1 year ago), with an update of this variable every 2 years.

We computed incidence rates of cholecystectomy by dividing the number of events by person-years of follow-up in each category. The relative risk was calculated as the incidence rate in a specific category of thiazide diuretic use divided by that in a specific reference group, with adjustment for age in 5-year categories. We used Cox proportional hazards regression¹⁰ to estimate multivariate relative risks of cholecystectomy using current age as the time scale and adjusting for body mass index (measured as weight in kilograms divided by the square of height in meters) at the beginning of each 2-year follow-up interval (continuous); weight change in the previous 2 years (weight loss ≥ 4.5 kg, weight loss of 2.3-4.49 kg, weight maintained ± 2.29 kg, weight gain of 2.3-4.49 kg, weight gain ≥ 4.5 kg); parity (0, 1, 2-3, ≥ 4 births); oral contraceptive use (ever, never); hormone therapy (premenopausal, postmenopausal without hormone therapy, postmenopausal with past hormone therapy, and postmenopausal with current hormone therapy); history of diabetes mellitus (yes, no); physical activity (quintiles); pack-years of smoking (0, 1-9, 10-24, 25-44, 45-64, ≥ 65); use of nonsteroidal anti-inflammatory drugs (0, 1-6, ≥ 7 times per week, and dose unknown); intake of energy-adjusted dietary fiber (quintiles); energy-adjusted carbohydrates (quintiles); daily alcohol intake (0, 0.1-4.9, 5.0-14.9, 15.0-29.9, ≥ 30.0 g); and daily coffee intake (0, 1, 2-3, ≥ 4 cups). All covariates were obtained or derived from the most recent questionnaire.

We conducted various analyses to address the possibility that an unconsidered factor related to the indication for anti-hypertensive therapy created spurious associations. We also ran a subanalysis that was adjusted for waist circumference (measured to the nearest quarter of an inch [0.64 cm] and obtained from the 1986 questionnaire). In addition, we tested whether body mass modified the association of thiazide use with cholecystectomy by entering the cross-product term for obesity (body mass index ≥ 30 [binary]) and thiazide diuretic use (never, past, current) along with the main effects terms for each. We used the same approach to evaluate whether any risk associated with thiazide diuretics varied across other potential risk factors for cholecystectomy. We evaluated the coefficients for the cross-product terms using the Wald test. All hypothesis tests were 2-sided and associations were considered to be statistically significant if the *P* value was less than .05. All analyses were conducted using SAS software, release 8.2 (SAS Institute, Cary, NC).

RESULTS

In our cohort, nearly 8% of the participants reported using thiazide diuretics at baseline. Women using thiazide diuretics maintained fairly consistent thiazide diuretic use throughout follow-up. The concordance between thiazide diuretics; use ranged from 34% to 65% from one biennial questionnaire to the next. We examined potential risk factors for cholecystectomy among nonusers and

users of thiazide diuretics to assess the potential for confounding (**Table 1**). Compared with nonusers of thiazide diuretics, users tended to be slightly heavier; they were substantially more likely to have a history of hypertension and to use other antihypertensive agents; they were more likely to have a history of diabetes; and they had more frequent routine physical checkups in the prior 2 years than nonusers. Users of thiazide diuretics were also slightly less physically active than nonusers.

During 1 419 903 person-years of follow-up from 1980 to 2000, we documented 8607 cases of cholecystectomy. Compared with nonusers of thiazide diuretics, the age-adjusted relative risk (RR) of cholecystectomy for users was 1.57 (95% confidence interval [CI], 1.49-1.66) (**Table 2**). After adjustment for body mass as a continuous variable, the multivariate RR was 1.30 (95% CI, 1.23-1.37). Additional adjustment for physical activity as a continuous variable had virtually no effect (multivariate RR, 1.29; 95% CI, 1.23-1.36). When we subsequently added history of hypertension to the model containing body mass and physical activity, the multivariate RR was 1.21 (95% CI, 1.14-1.28). Because adjustment for history of hypertension may have resulted in overcontrol of confounding, we did not include that variable in further models. When we adjusted for other potential risk factors for cholecystectomy the RR estimate was not substantially altered (multivariate RR, 1.24; 95% CI, 1.17-1.30). When we repeated our analysis after excluding women with a history of diabetes, the multivariate RR was 1.25 (95% CI, 1.19-1.32). Further adjustment for waist circumference among the subset of women for whom we had waist circumference data (n=3402) did not alter those results (multivariate RR, 1.24; 95% CI, 1.15-1.35). This suggests that body mass was the measured variable with the strongest potential for confounding.

To further address whether our findings for thiazide diuretics were due to an unconsidered factor that correlates with treatments for both hypertension and cholecystectomy, we evaluated the relation between use of antihypertensive agents other than thiazide diuretics and the risk of cholecystectomy. After mutually adjusting for use of thiazide diuretics and use of other antihypertensive agents, the multivariate RR of cholecystectomy for current use of β -blockers was 1.12 (95% CI, 1.02-1.22), for current use of calcium antagonists the multivariate RR was 1.09 (95% CI, 0.98-1.21), and for current use of angiotensin-converting enzyme (ACE) inhibitors the multivariate RR was 0.95 (95% CI, 0.84-1.08) compared with nonusers of these agents. The relation of thiazide diuretics to cholecystectomy risk was not confounded by any single or any combination of these 3 antihypertensive agents. In addition, the relations of use of β -blockers, calcium-channel blockers, and ACE inhibitors to risk of cholecystectomy were not confounded by each other or by thiazide diuretic use.

To investigate the possibility that our results were due to a generic effect of diuretics and not to a specific thiazide diuretics effect, we also examined the association between furosemide diuretics and cholecystectomy risk. Compared with nonusers of furosemide diuretics, the multivariate RR of cholecystectomy for current users of furosemide-type diuretics was 1.05 (95% CI, 0.83-1.31).

Table 1. Characteristics According to Current Thiazide Diuretic Use in 81 351 US Women Who Participated in the Nurses' Health Study*

Characteristic	Current Thiazide Diuretic Use	
	No	Yes
No. of participants at baseline	74 863	6488
Age at baseline, y	46	47
Body mass index†	24.8	26.9
Any weight loss in prior 2 y	30.2	32.4
Current smokers	23.4	23.5
Parity, No. of births	3.0	2.9
Use of oral contraceptives	50.2	52.4
Use of hormone therapy‡	70.2	71.7
History of hypertension	14.1	60.3
Use of furosemide diuretics	1.2	5.4
Use of β -blockers§	5.8	20.9
Use of calcium channel blockers§	2.8	8.0
Use of angiotensin-converting enzyme inhibitors§	1.9	8.2
History of diabetes	2.9	8.1
Physical activity, h/wk	3.0	2.9
Routine physical checkup in prior 2 y§	72.4	80.3
Mean daily intake		
Caffeine, mg	354	329
Alcohol, g	6.0	6.7
Polyunsaturated fat, g	10.4	10.4
Carbohydrates, g	188	186
Dietary fiber, g	16.6	16.8

*Values are given as percentage unless otherwise indicated. All values (except age) are standardized according to the age distribution of the cohort. All variables presented in the table (except number of participants and age) were updated using the most recent follow-up questionnaire.

†Body mass index was calculated as weight in kilograms divided by the square of height in meters.

‡Hormone therapy use among postmenopausal women only.

§Use of antihypertensive medication and routine physical checkups were assessed starting in 1988.

||Adjusted for total energy intake.

To examine whether latent symptoms of gallstone disease may have caused a discontinuation of thiazide diuretic use, thereby biasing our results, we repeated our analysis after excluding the first 4 years of follow-up and relating 1980 thiazide use to incidence of cholecystectomy from 1984 to 2000. Compared with nonusers, the multivariate RR for thiazide diuretic users was 1.22 (95% CI, 1.13-1.33). Similar results were observed when we excluded the first 8 years of follow-up and related 1980 thiazide use to incidence of cholecystectomy from 1988 to 2000 (multivariate RR for thiazide diuretic users compared with nonusers, 1.23; 95% CI, 1.13-1.34).

To address whether our results were explained by differences in medical surveillance according to thiazide diuretic use, we repeated our analysis after excluding women who did not have a routine medical checkup between 1986 and 1988. The multivariate RR comparing users with nonusers was 1.19 (95% CI, 1.07-1.31).

When we considered the 1982-2000 follow-up period and subdivided users of thiazide diuretics into past users and current users, current thiazide use showed a slightly stronger positive association with risk of cholecystectomy than past thiazide use (Table 2). Compared with never users of thiazide diuretics, the multivariate

Table 2. Relative Risk (RR) of Cholecystectomy in Relation to Thiazide Diuretic Use in the Nurses' Health Study*

	No. of Cases	No. of Person-years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
1980-2000 Follow-up Period				
Current thiazide diuretic use				
No	6446	1 187 894	1.0	1.0
Yes	2161	232 009	1.57 (1.49-1.66)	1.24 (1.17-1.30)
1982-2000 Follow-up Period				
Thiazide diuretic use				
Never use	5539	999 710	1.0	1.0
Past use	1145	120 774	1.46 (1.3761-1.55)	1.16 (1.08-1.24)
Current use	874	93 932	1.79 (1.66-1.92)	1.39 (1.29-1.50)

*Multivariate RRs of cholecystectomy were calculated using Cox proportional hazards regression with current age in years (continuous variable) as the time scale. The multivariate model included the following: body mass index (calculated as weight in kilograms divided by the square of height in meters) at the beginning of each 2-year follow-up interval (continuous variable); weight change in the previous 2 years (weight loss ≥ 4.5 kg, weight loss of 2.3-4.49 kg, weight maintained ± 2.29 kg, weight gain of 2.3-4.49 kg, and weight gain ≥ 10 kg); parity (0, 1, 2-3, ≥ 4 births); oral contraceptive use (ever, never); hormone therapy (women were categorized as premenopausal, postmenopausal without hormone therapy, postmenopausal with past hormone therapy, and postmenopausal with current hormone therapy); history of diabetes mellitus (yes, no); physical activity (quintiles); pack-years of smoking (0, 1-9, 10-24, 25-44, 45-64, ≥ 65); weekly use of nonsteroidal anti-inflammatory drugs (0, 1-6, ≥ 7 times, and unknown); intake of energy-adjusted dietary fiber (quintiles); energy-adjusted carbohydrates (quintiles); daily alcohol intake (0, 0.1-4.9, 5.0-14.9, 15.0-29.9, and ≥ 30.0 g); and daily coffee intake (0, 1, 2-3, and ≥ 4 cups). All covariates were updated using the most recent follow-up questionnaire.

Table 3. Relative Risk (RR) of Cholecystectomy (1982-2000) in Relation to Thiazide Diuretic Use in the Nurses' Health Study*

Thiazide Diuretic Use	No. of Cases	No. of Person-years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
Never use	5539	999 710	1.0 (Reference)	1.0 (Reference)
Past use, No. of years since last intake				
≥ 15	33	3456	1.31 (0.92-1.85)	1.11 (0.78-1.57)
10-14	152	15 951	1.25 (1.06-1.47)	1.02 (0.86-1.21)
5-9	256	25 080	1.45 (1.27-1.65)	1.15 (1.02-1.31)
2-4	497	54 333	1.48 (1.34-1.68)	1.16 (1.05-1.28)
1	207	22 029	1.63 (1.41-1.87)	1.27 (1.10-1.47)
P for trend†			.06	.35
Current use, No. of years since taking				
1	514	56 435	1.74 (1.59-1.91)	1.36 (1.24-1.49)
2-4	126	12 072	2.12 (1.77-2.55)	1.61 (1.35-1.93)
5-9	116	13 406	1.67 (1.39-2.02)	1.30 (1.08-1.57)
10-14	72	7096	1.86 (1.47-2.35)	1.40 (1.11-1.78)
≥ 15	46	4900	1.79 (1.34-2.41)	1.42 (1.06-1.91)
P for trend†			.96	.85

*The multivariate model included all variables listed in the footnote of Table 2.

†The test for trend did not include never users of thiazide diuretics.

RRs of cholecystectomy for past users was 1.16 (95% CI, 1.08-1.24) and the multivariate RR for current users was 1.39 (95% CI, 1.29-1.50).

We further subdivided past users into categories of decreasing time since past thiazide diuretic use and we subdivided current users into categories of increasing duration of current thiazide diuretic use (**Table 3**). No relation was seen between decreasing time since past thiazide diuretic use and cholecystectomy risk (*P* for test of trend for time since past thiazide use among past users, .35). Also, we observed no association between increasing duration of current thiazide diuretic use and risk of cholecystectomy (*P* for test of trend for duration of thiazide use among current users, .85).

To examine the possibility that current or past thiazide diuretic users differ from never users of thiazide diuretics with respect to unmeasured, potentially confounding variables, we repeated our analysis using past

users as the common reference group. Compared with past users, the risk of cholecystectomy was slightly increased among women with evidence of more recent initiation of thiazide diuretic use. The multivariate RR for women using thiazides for 1 year was 1.17 (95% CI, 1.05-1.31) and the multivariate RR for women using thiazides for 2 to 4 years was 1.39 (95% CI, 1.15-1.68). Although no statistically significant association was observed among women who used thiazide diuretics for 5 years or longer because of smaller numbers, the point estimates were similar to those for women with shorter duration of use (data not shown).

To evaluate the influence of thiazide diuretics on gallstone disease not requiring surgery, we excluded all cases with cholecystectomy and limited the analysis to cases of symptomatic but unremoved gallstones that occurred during the 1982 to 1986 follow-up period (**Table 4**). Compared with never users of thiazide di-

Table 4. Relative Risk (RR) of Newly Symptomatic Gallstones (1982-1986) in Relation to Thiazide Diuretic Use in the Nurses' Health Study*

Thiazide Diuretic Use	No. of Cases	No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
Never use	535	228 323	1.0 (Reference)	1.0 (Reference)
Past use	29	6515	2.76 (1.21-2.57)	1.36 (0.93-1.99)
Current use, No. of years since taking				
1	96	17 332	2.26 (1.81-2.82)	1.62 (1.29-2.04)
2-4	29	4823	2.46 (1.69-3.59)	1.81 (1.23-2.65)
5-9	27	5348	2.05 (1.39-3.03)	1.40 (0.94-1.09)
10-14	12	2444	1.95 (1.09-3.47)	1.35 (0.76-2.42)
≥15	4	1093	1.49 (0.56-4.03)	1.06 (0.39-2.88)
<i>P</i> for trend†			.44	.47

*The multivariate model included all variables listed in the footnote of Table 2.

†The test for trend did not include never users of thiazide diuretics.

uretics, the multivariate RR of gallstone disease was 1.36 (95% CI, 0.93-1.99) for past users and 1.57 (95% CI, 1.03-1.89) for current users. We found no relation for increasing duration of current thiazide diuretic use (*P* for test of trend for duration of thiazide use among current users, .47). In the analyses involving symptomatic gallstones, our data did not allow for stratification according to the number of years since discontinuation of thiazide diuretic use because cases of past users all fell into a single category of past exposure.

Because variability in thiazide diuretic use may be determined by body size, we examined the association between thiazide diuretic use and cholecystectomy within strata of current body mass index. The relation of thiazide diuretic use with cholecystectomy risk was suggestively more pronounced among nonobese women than among obese women (*P* for test of interaction, .10). Among women with a body mass index less than 30, the multivariate RRs of cholecystectomy for current and past users vs never users were 1.41 (95% CI, 1.28-1.55) and 1.24 (95% CI, 1.15-1.35), respectively. Among women with a body mass index greater than 30, the multivariate RRs of cholecystectomy for current and past users vs never users were 1.30 (95% CI, 1.15-1.48) and 1.01 (95% CI, 0.89-1.14), respectively.

We also investigated whether the apparent effect of thiazide diuretic use on incidence of cholecystectomy varied across strata of women based on other potential risk factors for gallstone disease. The associations between thiazide diuretic use and risk of cholecystectomy were similar across subgroups defined by age, recent weight change, parity, postmenopausal hormone therapy, and smoking status (all *P* values for tests of interaction >.1).

COMMENT

In this prospective study among women, current and past users of thiazide diuretics had a modest increase in the risk of cholecystectomy compared with never users. Our results argue in favor of a specific thiazide effect because we found no association between furosemide diuretic use and cholecystectomy. In addition, our results for thiazide diuretic use were not explained by concomi-

tant use of other antihypertensive agents such as β -blockers, calcium channel blockers, and ACE inhibitors.

Although our data are suggestive of a relation between thiazide diuretic use and risk of cholecystectomy, there are several plausible alternative explanations for our results. Because thiazide diuretic users in our cohort were characterized by multiple factors related to increased risk of cholecystectomy, such as increased body mass and decreased physical activity, a potential concern was the possibility that the apparent adverse effect of thiazide diuretic use on risk for cholecystectomy was due to the existence of a variable related to both hypertension and cholecystectomy. The fact that we observed rather disparate results before and after controlling for body mass and our observation of a slight increase in cholecystectomy risk among users of β -blockers makes it possible that an unconsidered factor related to hypertension could produce such confounding. We examined this possibility in various subanalyses by controlling for body mass and physical activity using continuous variables; by adjusting for history of hypertension; by adjusting for treatment with antihypertensive agents other than thiazide diuretics; by excluding women with a history of diabetes; by additionally adjusting for waist circumference; and by examining the relation of thiazide diuretic use to cholecystectomy risk within strata of obese and nonobese women. The association remained evident.

We were concerned about the possibility that the observed relations were due to detection bias, because women needed to see a physician to receive a thiazide diuretic prescription, leading to potentially greater diagnosis of subacute cholecystitis or gallstones and ultimately resulting in more cholecystectomies among these women. For example, thiazide diuretic use has been associated with asymptomatic elevations of serum amylase.¹¹ Thiazide users with asymptomatic increased serum amylase levels may have been more likely to be admitted to hospital for further workup, and cholecystectomies may have been preferentially performed in patients with mild acute cholecystitis coinciding with thiazide-associated elevations of serum amylase. The fact that thiazide diuretic users underwent more routine medical checkups than nonusers (Table 1) suggests the possibil-

ity of detection bias. In contrast to this possible explanation, the positive relation with cholecystectomy persisted when the analysis was restricted to women with regular checkups. Moreover, the number of unwarranted cases of cholecystectomy in our cohort would have had to be large to account for the observed results. Thus, increased gallstone detection resulting in more cholecystectomies among thiazide diuretic users is not likely to explain our results.

When we examined the relation of thiazide diuretics to risk of symptomatic but unremoved gallstones, no clear association was observed for increasing duration of current thiazide diuretic use. We were unable to address the association with time since past thiazide use. Thus, our results do not rule out the possibility that thiazide diuretics use are related to the early stages of gallstone formation. We have no information on whether thiazide diuretic use is related to risk of developing clinically asymptomatic gallstones, since the outcomes in our data set were limited to women with cholecystectomy or confirmed gallstones with accompanying symptoms.

Measurement error in our assessment of thiazide diuretic use was a potential concern because we lacked information regarding the validity of self-reported thiazide diuretic use. However, reporting of other lifestyle factors has been shown to have a high degree of validity and is reproducible in this cohort.¹²⁻¹⁴ Moreover, measurement error would tend to dampen results producing null findings but should not cause a positive association. Our study was limited by the absence of information regarding thiazide dosage, which prevented us from addressing the effect of increasing doses of thiazide diuretics on cholecystectomy risk. A further limitation was that our study was designed to assess thiazide diuretic use only in 2-year intervals. This limited our ability to precisely examine the association between shorter periods of exposure to thiazide diuretics in relation to risk of cholecystectomy.

Notwithstanding several limitations of our study, our findings are fairly consistent with results from 2 case-control studies^{4,5} that reported odds ratios (ORs) of acute cholecystitis for recent thiazide diuretic use of 2.0 (95% CI, 1.4-2.7) and 2.1 (95% CI, 1.1-3.9), respectively. Those 2 studies found no association among past thiazide users (OR, 0.8 [95% CI, 0.5-1.3] and OR, 0.9 [95% CI, 0.3-2.3], respectively). We observed a very weak association with past thiazide diuretic use, and the point estimate for past use in our study lies within the confidence bounds of the results of both those studies.^{4,5}

One case-control study⁶ evaluated the relation of recent thiazide diuretic use to risk of acute cholecystitis using data from the Boston Collaborative Drug Surveillance Program and the Group Health Cooperative of Puget Sound. In the Boston Collaborative Drug Surveillance Program series, recent use of thiazide diuretics was related to a suggestive increase in risk of acute cholecystitis (OR, 1.3 [95% CI, 0.7-2.3]), whereas in the Group Health Cooperative of Puget Sound series, recent use of thiazide diuretics showed no association with risk (OR, 0.9 [95% CI, 0.5-1.5]). The CI in each of these studies readily included our results.

One case-control study⁷ comparing women who had breast cancer with women diagnosed as having choleli-

thiasis found no difference in thiazide diuretic use between the 2 groups (crude OR, 1.09 [95% CI, 0.76-1.55]), suggesting no association between thiazide diuretics use and gallstones (given the lack of relation between thiazide diuretics use and breast cancer). One case-series of patients with acute pancreatitis⁸ found that diuretic use was suggestively greater among the subgroup of patients with gallstones than among those without gallstones. However, that study⁸ examined all diuretic use and not that of thiazide diuretics specifically, which could have hampered the study's ability to detect a potential association.

Our data did not allow us to address potential biological mechanisms relating thiazide diuretic use to increased cholecystectomy risk because the indication for cholecystectomy and the composition of the gallstones are unknown to us. A positive association between thiazide diuretic use and cholesterol gallstones is supported by one experimental study in humans showing that thiazides increase biliary cholesterol saturation.² In addition, thiazide diuretics induce glucose intolerance,¹⁵ leading to gallbladder hypomotility¹⁶—a condition that is associated with the development of both cholesterol and pigment gallstones¹⁷ as well as with acute acalculous cholecystitis.¹⁸ Thiazides, particularly when given in high dosage, may also increase plasma triglyceride and low-density lipoprotein levels,¹⁹ which have been linked to enhanced occurrence of gallstones.²⁰ Because thiazide diuretics frequently cause hypokalemia²¹ and hypomagnesemia,²² an adverse effect of thiazide diuretics on gallbladder disease could also be due in part to deficient levels of potassium and magnesium, 2 dietary factors that we found to show strong inverse relationships with gallstones and cholecystectomy (data not shown).

In summary, our findings are compatible with the hypothesis that the use of thiazide diuretics increases the risk of symptomatic cholelithiasis. However, we cannot rule out the possibility that our results are in part explained by unconsidered factors related to the indication for antihypertensive therapy or by differences in medical surveillance between thiazide diuretic users and nonusers. Further research is required to determine whether thiazides induce gallstone development per se or whether thiazides increase the risk of acute cholecystitis in subjects with prevalent gallstones.

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